

# A short critical history of the application of genomics to animal breeding

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## ABSTRACT

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SNPs

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Two scientific schools have been in coexistence from the beginning of genetics, one of them searching for factors of inheritance and the other one applying biometrical models to study the relationships between relatives. With the development of molecular genetics, the possibilities of detecting genes having a noticeable effect in traits augmented. Some genes with large or medium effects were localized in animals, although the most common result was to detect markers linked to these genes, allowing the possibility of assisting selection programs with markers. When a large amount of simple and inexpensive markers were available, the SNPs, new possibilities were opened since they did not need the presence of genes of large or medium effect controlling a trait, because the whole genome was scanned. Using a large amount of SNPs permits having a prediction of the breeding value at birth accurate enough to be used in some cases, like dairy cattle, to halve its generation interval. In other animal breeding programs, the implementation of genomic selection is less clear and the way in which it can be useful should be carefully studied. The need for large populations for associating phenotypic data and markers, plus the need for repeating the process continuously, complicates its application in some cases. The implementation of the information provided by the SNPs in current genetic programs has led to the development of complex statistical tools, joining the efforts of the two schools, factorial and biometrical, that nowadays work closely related.

## 1. The long and windy road to genomic selection

### 1.1. Genetics and animal breeding

From the beginning, there were two scientific traditions in genetics and in its applications to animal breeding. The first, which we can call molecular tradition, starts with Mendel and its aim is to locate and characterize from a biochemical point of view those factors that form the

genetic program, hoping to someday manipulate it for our benefit. The second, whose origin can be traced to Galton, and which we can call statistical tradition, studies the manifestation of the genetic program in the quantitative traits through the correlations among relatives with the objective of inducing a genetic-economic change in the productive traits. These two traditions have not been kept as two separate scientific schools but they intermix or separate depending on their respective achievements. Moreover, some prominent animal breeder like Alan Robertson could represent both traditions.

The study of enzymatic polymorphisms through electrophoresis opened new ways, in the 1960s, to investigate the genetic variation of animal populations, which in the case of livestock disposal, until then, of blood groups and

mutants of color as the unique genes of known inheritance (Neimann-Sorensen and Robertson, 1961). The electrophoresis allowed studying of genes independently on whether they show phenotypic variability or not, and revealed an increasing genetic variability. However, only a handful of genetic variants were detected due to the limitations of the technique.

### 1.2. The QTL explosion and deception

The advent of the new techniques of DNA analysis marks the beginning of the new field of genomics: the scientific discipline of mapping, sequencing and analyzing genomic level of DNA information. Taking advantage of polymorphic markers called microsatellites, spread throughout the genome, researchers were able to build genetic maps of domestic species and to search for regions of the genome harboring genes affecting the performance for economically important traits.

In the 1990s the QTL detection experiment started. Methods to detect these loci were reviewed by Andersson (2001). Initially, two basic designs were used. The first uses the linkage disequilibrium between markers and QTL generated by crosses. Typically, animals are generated by crossing breeds that are highly divergent for the traits of interest (for example European wild boar and domestic Large White or junglefowl and domestic White Leghorn chicken). The second design uses mainly the within-family linkage disequilibrium. This design is especially well suited for commercial populations as dairy cattle where large half-sib families are available. This activity has been very successful. In the data base <http://www.animalgenome.org/QTLdb/> the number of reported QTLs are 9862 affecting 653 traits (pigs), 8305 affecting 467 traits (cattle), 3919 for 297 traits (chicken) and 789 for 219 traits (sheep).

After detecting a QTL, the next task is to locate the gene responsible (causal mutation). In QTL detection studies, we can locate one QTL in a chromosome as a region of about 20–40 cM (probably harboring 200–400 genes) which made it difficult to identify the underlying gene responsible. To refine the position several actions can be taken: to increase the number of individuals, to carry out fine mapping or to try the 'candidate gene approach'. All these approaches are difficult, expensive in terms of time and money and success is not guaranteed, thereby making the location of the responsible gene a formidable task. Georges (2007) describes three successful stories: DGAT1 and ABCG2 that affect milk composition in cattle and IGF2 and MSTN influencing muscle mass in pigs and sheep, respectively. Notwithstanding, the difficulties for finding the causal mutations can be illustrated for example by more than 9000 QTLs reported in pigs, of which less than a dozen of causative mutations have been firmly established. Interestingly, the first QTL reported in livestock was FAT1 QTL located in swine chromosome 4 (Andersson et al., 1994); however, its causal mutation is still unknown.

### 1.3. Marker-assisted selection

One of the main motivations for QTL detection in domestic animals is Marker Assisted Selection (MAS).

The usual way of thinking of MAS is a three-step process. First, detect one or several QTLs. Second, find the gene responsible (causal mutation). Third, increase the frequency of the favorable allele either by selection or by introgression. There are some examples as the halothane gene in pigs or the Booroola gene in sheep. This strategy should better be called Gene Assisted Selection. Another approach is to use markers that are in linkage disequilibrium or linkage equilibrium with QTLs. All these applications, from a commercial point of view, were reviewed by Dekkers (2004).

The theory underlying MAS was clarified to a great extent by Lande and Thompson (1990). If the phenotype and the true QTLs for a trait were known, the advantage of QTL-selection response with respect to phenotypic selection would be  $1/h$ , where  $h$  is the square root of the heritability. Thus for heritabilities of 0.10, 0.25 and 0.50 the advantage would be huge: 316%, 200% and 140%, respectively. If markers explain just  $p$  percent of the additive variance the advantage would simply be  $\sqrt{p}/h$ . They also developed selection indices that combine individual and family phenotypic information and molecular scores. In the paper the authors assume that linkage disequilibrium among markers and QTLs is the key factor for the success of MAS and therefore they consider a cross population as the more appropriate one.

The impact of MAS in livestock breeding programs has been modest because the QTL that exceeds the chosen significance thresholds usually accounts only for a minor fraction of the trait variance. However, Smith and Smith (1993) stressed that the number of markers was the only limitation for the success of MAS, even in panmictic populations. They realized that it would be a question of time that enough number of markers were available and urged labs to accomplish the task.

## 2. Genomic selection

### 2.1. Many available markers at an affordable cost

Meuwissen et al. (2001) proposed what nowadays is called *genomic selection*. It is rooted in two assumptions that now have been accomplished. The first is that panels with tens of thousands of markers will be available together with cost-effective genotyping procedures, and the second is that marker-density will be sufficient for all responsible genes of a trait to be in linkage disequilibrium with flanking markers. Genomic projects in several domestic species have allowed a large numbers of SNPs to be discovered as a by-product of sequencing or in subsequent re-sequencing. Although we are still far from latest human SNP chips with over 3000,000 SNPs, commercial 'SNP chips' exist for cattle (750,000), dogs (250,000 SNPs), sheep (56,000 SNPs), pigs (60,000 SNPs), horses (55,000 SNPs) and chickens (600,000 SNPs) that can be easily genotyped using the same well-established technology as in human and at a reasonable cost.

In the simplest terms, genomic selection is a two-step process. First, estimate the effects of markers ( $> 50,000$  SNPs) in a reference (training) population that has been phenotyped and genotyped. Second, use this information to predict the

breeding value of candidates to selection in a testing (evaluation) population that has been only genotyped for the previous markers. Conceptually, the main difference between genomic selection and MAS is that genomic selection uses a panel of dense markers so that all QTLs are in linkage disequilibrium with at least one marker. For this reason some authors call it Genome Assisted Selection. However, although the [Smith and Smith \(1993\)](#) prediction that MAS would be a fact when the number of markers were huge was prophetic, other predictions, such as no new sophisticated statistical methods would be needed, have clearly failed. Genomic selection made its advent together with a galaxy of new statistical and computational methods basically dealing with what is usually called the “large  $p$  and small  $n$  problem”; i.e., how to analyze problems where the number of variables are far more larger than the number of observations.

## 2.2. How many SNPs?

The continuous decreasing of genotyping costs permits one to predict that in the near future higher density chips and finally the whole genome will be available. However, it seems that the predictive capacity of having the whole genome sequenced will not be much higher than the one obtained by using the current 50,000 SNPs markers. In a recent research with *Drosophila*, [Ober et al. \(2012\)](#) showed that the predictive ability using the whole genome (2.5 million SNPs) was the same as using 150,000 SNPs. In dairy cattle [Van Raden et al. \(2011\)](#) obtained a gain in reliability of only 1.6% when using 500,000 markers instead of 50,000, and using imputation techniques even low-density marker panels (3,000 SNPs) can produce a similar predictive ability in dairy cattle ([Berry and Kearney, 2011](#)) and pigs ([Welmann et al., 2013](#); [Cleveland and Hickey, 2013](#)). However, there is a twofold advantage in using the whole sequence; the first is that we will be sure that all QTL will be included and therefore deterioration of linkage disequilibrium along generations could be alleviated ([Meuwissen and Goddard, 2010](#)), and the second is that multibreed evaluations could be probably more precise. Both topics need to be investigated more deeply; for example, causal mutations are expected to be originated in a breed or a line, but not in other breed; thus predictions from one population will not apply to another population; in any case the sequence depth will be critical ([Pérez-Enciso, 2014](#)). Another advantage of using the whole sequence is avoiding the ascertainment bias originated by marker preselection. Markers are preselected with the aim of segregating, which produces an overestimation of variability, affecting the estimated relationship between individuals. When the whole sequence is used, this problem vanishes.

## 2.3. The promises of genomic selection

Genomic selection has been met with a lot of enthusiasm and some breeding companies are re-designing their breeding programs. The idea is that using genomic selection we can potentially predict the breeding values for selection candidates at birth with a higher accuracy than the classical pedigree index. Consequently we can select

animals at an early age and it is expected in some cases to double the rate of genetic improvement per year. For example, in dairy cattle an optimal breeding design with genomic selection will be more or less as follows:

- (a) Genotype a large number of bull calves from the population.
- (b) Calculate GEBVs for these calves (accuracy=0.8).
- (c) Select a team based on GEBV and sell semen from these bulls as soon as they can produce it. The generation interval will be reduced from ~4 yrs to ~2 yrs and the rate of genetic gain will be doubled.

In prolific species the advantages of using genomic selection are much less clear. The schemes of animal breeding are based on selecting in nuclei of selection to provide animals to the multipliers that will provide crossbred females and sometimes crossbred males to the commercial farms. In these schemes genomic selection will not have its main effect by reducing the generation interval, since no progeny test is performed. Moreover, the sires and dams have a much lower value than dairy cattle, preventing the use of genomic selection due to its cost. However, some simulation studies have shown that genomic selection can be cost-effective in pigs using imputation techniques ([Cleveland and Hickey, 2013](#)), and [Lillehammer et al. \(2013\)](#) estimate an increase in genetic progress – about 10% higher when using genomic selection in pigs in national Norwegian program.

## 3. Difficulties in implementing GS

### 3.1. The need of large training populations

The first problem encountered when working with GS is the need of having accurate enough equations to relate SNPs with phenotypic information. Large training populations are required to obtain acceptable accuracies for breeding values ([Goddard and Hayes, 2009](#)). Training populations can be composed of several thousand animals in dairy cattle ([Wensch-Dorendorf et al., 2011](#)), but selection nucleus in rabbits and pigs are often composed of 12–20 males and 120–250 females per line; thus the effective population number for reproductive traits may be very small, and even for growth traits it will not be easy to collect a large number of animals for the training population, a problem that can also take place in birds, even for larger nucleus sizes. Although there are some national programs in pigs, the difficulty of needing a large training population remains, even when phenotyping is easy as in litter size, because low heritability traits require larger training populations. [Haberland et al. \(2013\)](#) suggest a minimum number of 1000 animals in a training population in pigs. Several strategies have been proposed for national programs ([Lillehammer et al., 2013](#)), and some strategies can be examined implying larger training populations by using several generations ([Chen et al., 2012](#)), or animals from multipliers, which are closely related to the nucleus animals. Effectiveness of GS is higher when the training population and the animals to be selected are closely related; the use of GS for unrelated animals would require fantastic figures for training populations ([Meuwissen, 2009](#)).



### 3.2. The need of continuous phenotyping

One of the expectations generated by GS was the use of it in traits that are expensive or difficult to measure, for example meat quality traits. Selection produces LD between the markers and the QTLs affecting the traits and GS is based in using these associations to avoid measuring the expensive traits. However, some meat quality traits are scarcely related to traits that are selected, and in any case the LD is being lost generation after generation. Some simulation experiments have shown that accuracy using the same markers is rapidly lost generation after generation and new training populations are required (Sonesson and Meuwissen 2009; Ibañez and Blasco 2011). When continuous phenotyping is required and large training populations are needed, GS becomes less attractive for traits that are expensive to be measured.

### 3.3. New problems for genetic evaluation

The use of genomic information presents new problems in predicting breeding values. Genetic evaluation in commercial programs is nowadays widely based in BLUP, ensuring unbiased estimates if the full relationship matrix and all data used in selection are included in the evaluation. Preselecting bulls in dairy cattle using genomic information can lead to biased predictions with lower accuracy, as has been noted by Patry and Ducrocq (2011), leading to a decrease in genetic progress and distorting international dairy bulls comparisons (Patry et al., 2013). Integrating genomic and phenotypic information for predicting breeding values in a single step has been proposed by Legarra et al. (2009), but the computing cost is much higher and requires specific strategies for solving the equations (Legarra and Ducrocq, 2012). Including non-additive effects in the model or nonlinear traits as longevity produces further complications. An intensive research is now being developed in this area, and the progress of computing speed and capacity will also help in solving problems that now a days prevent the implementation of these solutions.

### 3.4. The lack of robustness of simulation studies

The interest of using genomic selection has been mainly examined by simulation experiments, as formerly happened when examining the interest of marker-assisted selection or the use of QTLs in selection programs. Useful as they are, simulation experiments represent a simplification that sometimes can lead to different conclusions when the parameters used in the simulation change; therefore, these experiments should check the robustness of the conclusions and avoid presenting excessively favorable frames for genomic selection. These favorable expectations appear when the training population and the population in which genomic selection is evaluated are too close, when genetic parameters are excessively optimistic, when the model for generating the data and the model for analyzing it are the same, etc. For example, often an additive model generates the data and an additive model analyzes the results; in this case it might be interesting to check the robustness of the simulation by

generating data with non-additive genetic effects, common environment not considered, interactions genotype  $\times$  environment, etc., and analyze results with the usual additive model. Non additive interactions can be difficult to analyze; for example, García-Cortés et al. (2014) have shown that with inbreeding, the coefficient of dominance cannot be estimated with biallelic markers such as SNPs. And as Schaeffer (2006) said, if epistatic effects are large, then the accuracy of genomic breeding values may never reach 0.75 (Schaeffer, 2006).

Another example is the use of excessively optimistic genetic parameters; for example, Piles et al. (in press) reviewed the response to selection in rabbit experiments, and the actual responses obtained were consistent with the values of heritabilities of 0.03 instead of the heritability of 0.10 often used for simulation experiments. In pigs, response to selection for litter size has been variable (see review in Blasco et al., 1995), showing that it is difficult to choose a single value of the parameter for simulation experiments. The efficacy of genomic selection when heritabilities are very low is questionable, since extremely large training populations are needed and low accuracy equations are obtained, which can add little to the accuracy obtained by classical methods. Checking the robustness of the simulation experiments would permit to generalize their results further than the precise circumstance that the simulation describes.

### 3.5. Implanting GS in current breeding schemes

Some of the difficulties for implanting genomic selection come from the characteristics of current breeding schemes. In prolific species, selection is performed in relatively small selection nucleus in which several lines are selected for several traits in order to produce a crossbreeding female and sometimes a crossbreeding male. Often the benefits of genomic selection are referred to a single trait which was the object of a simulation experiment or an analysis with real data; however, the benefits of genomic selection should be evaluated considering not only its efficiency in improving the accuracy of one trait, but also its contribution to the genetic response on the aggregated genotype; i.e., on the economic additive value. For example, genomic selection can improve the accuracy on food conversion rate having an important effect on the response to selection for this trait (González-Recio et al., 2009); but often the genetic correlation between food conversion rate and growth rate is high; therefore if both traits are included in the selection index, as they usually are, the improvement in the aggregate genotype obtained by using genomic selection for food conversion rate is more limited. Some traits currently used in breeding programs have a high heritability (for example, fat content in pigs) or an extremely low heritability (for example, litter size in rabbits and to some extent in pigs). In both cases the benefits of genomic selection are less clear than in dairy cattle. Undoubtedly, the prestige of using genomic selection can modify the market quota of some companies, constituting genomic selection a value in itself, but the discussion of its impact in the market is out of the limits of the present review.

### 3.6. The cost of genotyping

Cost of genotyping has been dramatically reduced in the last few years, allowing the implantation of genomic selection in dairy cattle in many countries at a reasonable cost. In general, 45,000 SNPs are used in bulls and low-density 3000 SNPs chips are used for genotyping cows, heifers, and calves on commercial dairy farms for less than \$50 per animal (Van Eenennaam et al., 2014) using imputation techniques. Nevertheless, the cost is still important enough to prevent using extensive genotyping in some species in which the breeding animal has a low value and several lines are used for the final crossbred product, like rabbits, pigs and poultry. Van Eenennaam et al. (2014) discuss some possible cost-effective implementation of genomic selection in pigs and poultry, based on the use of low density chips and imputation, but standard solutions are far to be clearly established and research is still needed on how to implement at least some aspects of genomic selection in these programs. The need of large training populations that should be constituted for each line, and the need of high-density chips to construct the imputations can prevent the use of genomic selection for commercial purposes in these species attending only to the current economic cost. All costs should be considered before starting a genomic selection program, including the costs associated with the delay in recovering the investment in the training population.

### 4. The resurrection of the QTLs detection

The development of the platforms of high-density genotyping has hurled new impetus to the gene detection area in the form of what is called Genome-wide association studies (GWAS) that try to use this huge number of markers to locate the causal genes. Although in some sense the genomic selection is related with the GWAS, there is a difference in the focus. In GWAS the aim is to decipher the genetic base of quantitative traits whereas in genomic selection the objective is to predict the genetic values of candidates to selection to choose the parents of the next generation. The GWAS strategies are now being implemented in livestock species although for the moment they only have been successful in traits controlled by one or few genes, such as the gene *MITF* that causes white spots in dogs or the *SLC65* and *ABCA12* that cause congenital muscular dystocia in cattle.

The large amount of GWAS studies in the last few years, particularly in human genetics, has been followed by some disappointment when many of the associations of important traits with SNPs disappeared when using larger samples or more detailed studies. Excessive expectations of GWAS results are generated by different causes. One of them is the lack of major genes determining most of the traits of interest; it seems that most traits are determined by many genes of small effects and large effect genes are usually fixed in selected populations. Another reason is the misinterpretation of the amount of evidence provided by statistical tests. In a recent paper, using the Bayesian theory Johnson (2013) showed that in order to obtain an evidence of 95% of probability, the *P*-value needed is about

0.005; if multiple test techniques are applied for individual *P*-values of 0.005, many SNP associations would disappear. Even the meaning of the *P*-values offered by GWAS studied has been questioned due to the bias introduced by ignoring the linkage disequilibrium among all markers and all causal genes; this bias also overestimates the variance explained by the gene detected by GWAS (Gianola et al., 2013). Another problem of GWAS studies derives from the fact that linkage disequilibrium can be produced by statistical association between an SNP and a causal gene instead of by real linkage between the SNP and the gene, i.e., an SNP can be in linkage disequilibrium with a causal gene although they are in different chromosomes. A list of criticism of GWAS has been recently reviewed by Visscher et al. (2012), and some limitations and pitfalls in the analyses have been commented by Wray et al. (2013); nevertheless, the conclusion of Visscher et al. (2012) is that the balance of GWAS is clearly positive in human medicine. As the amount of genotypic data gathered for genomic selection increases exponentially, it may happen that in the future more weight will be given to SNPs associated with known genes and less weight to others that seem to be irrelevant, as some methods of genomic selection propose.

### Conflict of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by both named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by both of us.

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